HISTOPLASMOSIS

A Review of Three Cases Studied in San Diego County

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■ *Three cases of histoplasmosis, a disease seldom reported in California, were diagnosed clinically by the authors in San Diego County. It is probable that there is a higher incidence of this disease in California than is at present recognized.*

Travel history, histoplasmin skin testing and serologic studies for mycotic infection are important in the diagnosis. Cultures of secretions and biopsy material are of great value if positive; but negative cultures (at least in non-endemic areas) do not rule out the disease. Travel and migration to and from endemic areas present opportunities for this disease to constitute a diagnostic problem far from the geographic area in which the disease was acquired.

Although usually benign, histoplasmosis may be severe in the acute state, may disseminate or may be chronically active and progressive. Amphotericin B is the only effective chemotherapeutic agent and it is usually reserved for these forms of the disease.

MANY EXCELLENT PAPERS thoroughly cover histoplasmosis in endemic areas.* Loosli,[20] estimated that 30 million people in the United States are infected with histoplasmosis capsulatum. Fungal infections now rank fourth in the United States as cause of death from infectious diseases.[16] Histoplasmosis is known to occur in California and it is possible the incidence is much higher than is recognized. A high index of suspicion is important in atypical cases since histoplasmosis may simulate more common diseases. In the present age of swift travel and constant migration, histoplasmosis must always be considered by physicians anywhere in the United States and particularly in California in light of the great influx of new people. We can no longer consider the Mississippi River Basin as "the endemic area." Surveys in "non-endemic areas" show positive skin reactions in as many as 70 per cent of persons tested.[5] Yet, review of CALIFORNIA MEDICINE and of *California and Western Medicine* for the period 1936-1965 revealed only two reports dealing with three cases of active histoplasmosis. Diagnosis was by lung biopsy in one case, one by x-ray films of the chest, skin tests, serologic studies and residence history, and one by autopsy.

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Reports of Cases

Following are reports of three additional cases discovered in San Diego County. Each is different from the others roentgenologically and clinically.

CASE 1.—A nine-year-old white girl had dry cough, malaise and slight fever in June 1962. She had lived on the west coast all her life but in May 1962 visited Kansas City, Missouri. While there she spent several hours in an abandoned chicken coop playing with newborn puppies. Results of hematologic studies were within normal limits except for the blood sedimentation rate which was 42 mm in one hour. An x-ray film of the chest showed a widened mediastinum and multiple 1 cm radiopaque soft-bordered nodules scattered in both lung fields (Figure 1). Histoplasmin skin tests were weakly positive. Tests with purified protein derivative No. 2 and coccidioidin 1:100 were negative. A scalene node biopsy also was negative. Histoplasmosis complement fixation was positive (1:256).

After two months' bed rest followed by limited activity for several months, partial clearing was noted and the sedimentation rate decreased. In August 1963 low grade fever and malaise again developed and there was an increase in the scattered nodular infiltrates and persistence of the widened upper mediastinum. Several weeks of bedrest again was followed by improvement as observed by serial x-ray films, resumption of normal temperature and decrease in the sedimentation rate. In September 1964, after an interval improvement, new infiltrates were again noted roentgenographically. After three months' bedrest roentgen studies still showed progression of disease. These findings were accompanied by fever, malaise, dry cough and blood sedimentation rate ranging between 40 and 50 mm in one hour.

Treatment with amphotericin B was begun in January 1965 at a dose of 1 mg per kg of body weight. By late March 1965, the patient had received a total of approximately 0.8 gm (more than 25 mg per kg of body weight). Serial x-ray films showed distinct partial clearing of the nodular pulmonary infiltrates and some decrease in the extent of mediastinal involvement. The symptoms completely abated during treatment with amphotericin B and the sedimentation rate decreased from 42 mm to 22 mm. A slight elevation of the blood urea nitrogen occurred and hemoglobin decreased 20 per cent.

During the summer of 1966 low grade temperature elevation and malaise again occurred, persisting several weeks. In September the temperature decreased to normal range, the patient was feeling well but histoplasmosis complement fixation was still positive at 1:128. It appeared that further chemotherapy might be required.

CASE 2.—An eight-year-old white boy had onset of symptoms in September 1959. Although born in San Diego, the patient had visited Kentucky in June 1959. While there, he helped gather eggs in a chicken house. A skin test with histoplasmin 1:100 was strongly positive in October 1959. Radiographs of the chest (Figure 2) showed infil-

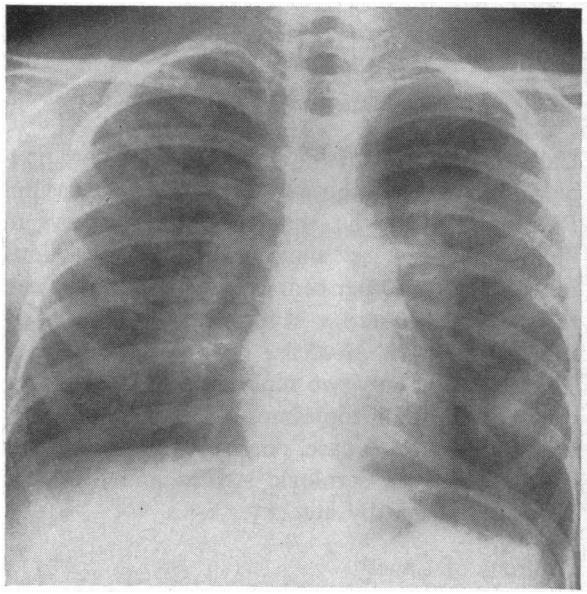

Figure 1.—(Case 1) Multiple nodular infiltrates are scattered in both lung fields. There is rather pronounced widening of the upper mediastinum attributed to enlargement of the hilar and mediastinal lymph nodes.

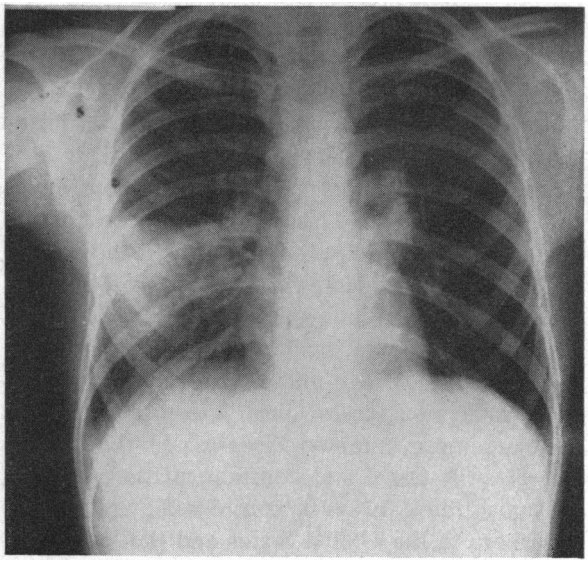

Figure 2.—(Case 2) The right hilar structures are enlarged as are the left hilar structures to a lesser degree. Dense clouding throughout the region of the right middle lobe.

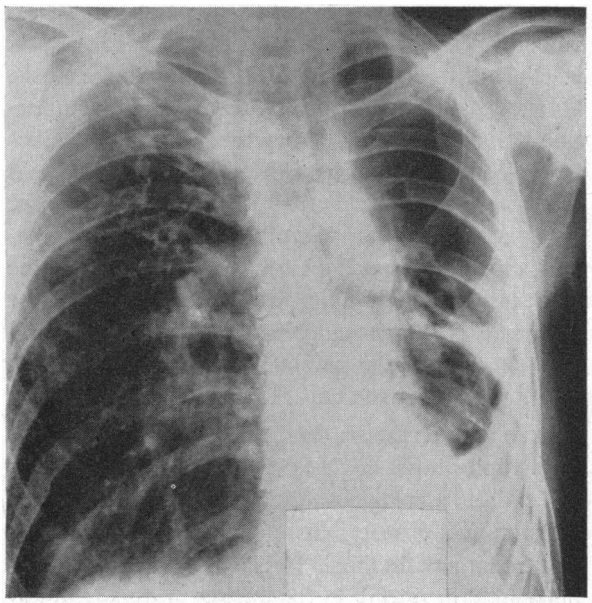

Figure 3.—(Case 3) A large aircontaining structure presumably a cavity, occupies about two-thirds of the left lung field. A smaller cavity approximately 4 cm in diameter is situated in the right upper lung field. Numerous fine infiltrates throughout the remainder of the lung.

tration and/or atelectasis of the right middle lobe with bilateral hilar adenopathy. Tests with PPD No. 2 and coccidioidin 1:100 were negative. Histoplasmin skin test (1:100) was positive. Complement fixation was positive (1:256 titer) for histoplasmosis and negative for coccidioidomycosis.

At last report (May 1963) the patient appeared to have had prompt and complete recovery with no treatment other than bed rest in the fall of 1959. This case is an example of benign pulmonary histoplasmosis.

CASE 3.—A 57-year-old white man who had lived in Illinois and Missouri until 1950 complained of cough, loss of weight, weakness and expectoration. The cough began in 1941 and in 1958 he became unable to work. He had not been east of the Rockies since 1950. Radiographs of the chest (Figure 3) showed extensive infiltration in both lungs, the left lung largely destroyed by cavitary disease. Except for a positive reaction to histoplasmin, all skin tests were negative. Multiple sputum cultures in several laboratories were negative for tubercle bacilli and fungi. Mouse inoculation of sputum by one of the authors at San Diego State College identified the pathogen as histoplasma capsulatum. These findings were confirmed by culture at the Kansas City field station of the U.S.P.H.S. and by complement fixation titer of 1:512. Serologic titers for coccidioidomycosis were negative.

Studies of this patient at San Diego County Hospital 1960 to 1963 showed the disease still active. Complement fixation titer was 1:256. Sputum cultures again were negative. (The patient has since died in a custodial hospital.) This case indicates that eight years away from an endemic area does not preclude the presence of serious histoplasmosis. There was no history of corticosteroid therapy, and no evidence of debilitating underlying disease (such as lymphoma) which might activate histoplasmosis was noted during four years of observation.

Extrapulmonary dissemination apparently did not occur in any of these three cases.

Clinical Features

Conrad and coworkers[8] described histoplasmosis as a disease of protean manifestations. Case 1 is an example of non-cavitary, chronically active, progressive pulmonary histoplasmosis with considerable involvement of mediastinal lymph nodes. Case 2 is an example of benign pulmonary histoplasmosis with mediastinal lymph node involvement spontaneously clearing. Case 3 is an example of the chronic progressive cavitary-type which, untreated, frequently results in death.[12,18,19]

The most common form of histoplasmosis, no doubt, is the more completely benign form with no clinical or subjective manifestations, resulting in a positive histoplasmin skin test and frequently in pulmonary calcifications.[31] The disseminated form has the poorest prognosis and most frequently attacks young[6,9] and debilitated elderly persons. The early recognition of dissemination is imperative so that therapy can be begun. Pulmonary histoplasmosis may present as an apparently inactive form of the disease. Some patients, however, show very slow progression by roentgen examination and complement fixation titers.[35] Histoplasmosis is the most frequent cause of benign pulmonary granuloma.[9] It is not surprising that 10 per cent of the patients in tuberculosis sanitoria have unrecognized histoplasmosis,[31] either alone or existing with tuberculosis, since the chronic active progressive form is roentgenographically indistinguishable from cavitary tuberculosis. Twenty per cent of this group with unrecognized disease have negative histoplasmin skin tests and 10 per cent have negative serologic tests. Recog-

nition is imperative since this form of disease is progressive and, without treatment, fatal.[31] The less common manifestations of histoplasmosis are Addison's disease,[9] endocarditis,[27] pericarditis,[17] mediastinitis and superior vena caval obstruction.[33] Perhaps many of the "idiopathic" diseases of the heart and the fibrosing lesions of the mediastinum and retroperitoneum are in reality manifestations of histoplasmosis. Likewise, sarcoidosis is simply a non-caseating granulomatous reaction which in appearance is exactly like the non-caseating granulomatous reaction of histoplasmosis. Finally, bronchiectasis is a very common sequela of histoplasmosis.[36]

Incubation Period

In various epidemics reported (that is, in so-called endemic areas) the incubation period varies from four to 21 days.[13,24,28] It would appear that this varies according to the host reaction. In Case 2 reported herein, four months elapsed between brief exposure (1 June 1959) in an endemic area and the first symptoms (September 1959).

Diagnosis

Diagnosis may be laborious and baffling. Culture either on artificial media or by mouse inoculation is the surest method, and it is far from certain; even in active cases only 50 to 60 per cent of multiple cultures are positive. Since highly skilled, experienced microbiologists are a prime requisite, this diagnostic approach is frustratingly unreliable in non-endemic areas. Yeast bodies can alter the organisms morphologically and they may be encapsulated for years.[36] At certain phases the organisms cannot be grown by present methods. When the organism is grown from contaminated material, the media must have streptomycin and penicillin added. Once these antibiotics were thought to inhibit pyogenic contaminants, but now it is known that these substances enhance the growth.[6] Obviously, therefore, the use of either streptomycin or penicillin in vivo is contraindicated. Sputum cultures are worthless unless a lung lesion has a bronchial extension.

Skin testing is an important aid in diagnosis. The purport of the reaction is like that of the reaction to tuberculin in patients with tuberculosis, but anergy occurs more frequently than in tuberculosis, particularly in histoplasmosis of disseminated type.[6] In short, skin reaction is useful epidemiologically but a negative test does not preclude the disease. Negative skin tests for tuberculosis and coccidioidomycosis are also helpful in the differential diagnosis of histoplasmosis. However, since even in severe coccidioidal infection the skin test may be negative, serologic studies for coccidioidomycosis should also be done, as they were (with negative results) in the three cases herein reported. Serum for complement fixation should be drawn before or at the time of the skin test, because skin testing done before the specimen is drawn can bring about positive complement fixation in an inactive case or increase the titer in a proven case.[22]

Serologic testing is the touchstone for diagnosis of histoplasmosis in cases of lung disease of doubtful cause. Serologic findings must be correlated with clinical history, history of travel, skin tests and roentgen findings. It is useless to do histoplasmin skin testing in diagnostic problems unless serologic studies are also done if the reaction is positive. In spite of disagreement among authorities as to what constitutes a positive complement fixation tests, a titer of less than 1:8 seems of little diagnostic significance and higher than 1:64 always significant.[12,30] Serologic tests are usually positive during active disease and remain positive for a variable duration up to a year or more. A high rising titer is a good indication of active disease.[1] On the other hand, negative tests are not unusual in the presence of active disease.

The problem is further complicated, particularly for California physicians, since serologic cross reactions occur with coccidioidomycosis and blastomycosis. In fact, the authors of a report on one large series of young adults state that "all or most of the histoplasmin sensitivity found in California, Arizona and New Mexico probably represents cross sensitization by infection with coccidioides immitis.[21] Even though California is an endemic area for coccidioidomycosis, the patient's geographic history is important (although of decreasing value because of the widespread dissemination of the histoplasmosis capsulatum organism). In the past, coccidioidomycosis titers of 1:32 or greater were considered to signify possible dissemination, and the higher the titer the worse the prognosis. However we have observed several cases in which titers were higher than 1:32 and the patients recovered without dissemination. It is in the mild cases of coccidioidomycosis, where the complement fixation tests may be low or undetectable, that differential diagnosis becomes a test

of acumen although not actually a problem, since the patients are not ill. In addition, in proven cases of histoplasmosis with a titer of 1:160 or more, the reaction to coccidioidin is never greater than 1:20.[4] Recent studies of the fluorescent antibody inhibition test for histoplasmosis may improve the serologic diagnosis. At any rate the standardization of the test will be improved.[15]

There is no definite characteristic roentgenographic appearance associated with histoplasmosis. Roentgen studies contribute most when serial radiographs are correlated with the clinical course and laboratory studies.

Epidemiology

The mode of infection is by inhalation of the fungus from exogenous sources in nature. Apparently it is high organic content of bird excreta which promotes growth of the fungus in soil, and birds do not necessarily have or carry the active disease.[13] The fowl family, even the common starling, has been indicted as a carrier of this organism in the excreta.[25] At any rate, histoplasmosis has been cultured from soil at random.[10] This is not surprising, since histoplasmosis is the most common fungous disease of the animal kingdom.[38] Even so, epedemiologic surprises still occur—to wit, the report of a case in Great Britain in a person who had never been out of the country and had nothing to do with soil, animals or fowl. Only 14 other cases have been reported in England and surprisingly five of these were of the acute disseminated form.[23] On the other hand, among the natives of Panama the incidence of positive skin reaction to histoplasmin is high but the disease is rarely manifested clinically.[34] Very often the source of infection in infants is unknown, since they are not likely to have had contact with soil, particularly those who have not left the hospital since birth. In one case, feathers in a pillow were proved to be the source of infection in an infant.[11]

Treatment

Treatment of this disease is reviewed in many articles[2,29,32,37] as well as textbooks of pharmacology. Amphotericin B given intravenously appears to be the only effective antifungal agent currently available commercially. A total dosage of 25 mg per kg of body weight given over a period of several weeks is usually required when treatment is necessary. The toxicity of amphotericin B is such that it is indicated principally in severe acute infections, in chronic active disease and in the disseminated forms of histoplasmosis.

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